

1 **HIGHLIGHTS OF PRESCRIBING INFORMATION**
2 **These highlights do not include all the information needed to use**
3 **RYZODEG 70/30 safely and effectively. See full prescribing information**
4 **for RYZODEG 70/30.**

5
6 **RYZODEG® 70/30 (insulin degludec and insulin aspart injection), for**
7 **subcutaneous use**
8 **Initial U.S. Approval: [2015]**

9 -----INDICATIONS AND USAGE-----
10 RYZODEG 70/30 is an insulin analog indicated to improve glycemic control
11 in adults with diabetes mellitus (1).

12
13 Limitations of Use:
14 Not recommended for treating diabetic ketoacidosis.

- 15 -----DOSAGE AND ADMINISTRATION-----
- 16 • DO NOT dilute or mix RYZODEG 70/30 with any other insulin products
 - 17 or solutions (2.1).
 - 18 • Rotate injection sites to reduce the risk of lipodystrophy (2.1).
 - 19 • Individualize dose based on type of diabetes, metabolic needs, blood
 - 20 glucose monitoring results and glycemic control goal. (2.2, 2.3, 2.4, 2.5).
 - 21 • Administer subcutaneously once or twice daily with any main meal (s)
 - 22 (2.2).
 - 23 • Administer a rapid- or short-acting insulin at other meals if needed (2.2).
 - 24 • Patients with type 1 diabetes will generally require a rapid-or short-acting
 - 25 insulin at meals when RYZODEG 70/30 is not administered (2.2).
 - 26 • Adjust the dose according to fasting blood glucose measurements (2.2).
 - 27 • The recommended time between dose increases is 3 to 4 days (2.2)
 - 28 • Converting from other insulin therapies may require adjustment of timing
 - 29 and dose of RYZODEG 70/30 (2.4, 2.5).

30 -----DOSAGE FORMS AND STRENGTHS-----
31 RYZODEG 70/30 100 units/mL (U-100) available in:
32 • 3 mL FlexTouch® (3)

33 -----CONTRAINDICATIONS-----
34 • During episodes of hypoglycemia (4).
35 • Hypersensitivity to RYZODEG 70/30 or one of its excipients (4).

36 -----WARNINGS AND PRECAUTIONS-----
37 • *Never share* a RYZODEG 70/30 FlexTouch pen between patients, even if
38 the needle is changed (5.1).

- 39 • *Hyper- or hypoglycemia with changes in insulin regimen:* Carry out under
- 40 close medical supervision and increase frequency of blood glucose
- 41 monitoring (5.2).
- 42 • *Hypoglycemia:* May be life-threatening. Increase monitoring with
- 43 changes to: insulin dosage, co-administered glucose lowering
- 44 medications, meal pattern, physical activity; and in patients with renal
- 45 impairment or hepatic impairment or hypoglycemia unawareness (5.3,5.4,
- 46 6.1).
- 47 • *Hypoglycemia due to medication errors:* Accidental mix-ups between
- 48 insulin products can occur. Instruct patients to check insulin labels before
- 49 injection. DO NOT transfer RYZODEG 70/30 into a syringe for
- 50 administration as overdosage and severe hypoglycemia can result (5.4).
- 51 • *Hypersensitivity reactions:* Severe, life-threatening, generalized allergy,
- 52 including anaphylaxis, can occur. Discontinue RYZODEG 70/30, monitor
- 53 and treat if indicated (5.5).
- 54 • *Hypokalemia:* May be life-threatening. Monitor potassium levels in
- 55 patients at risk for hypokalemia and treat if indicated (5.6).
- 56 • *Fluid retention and heart failure with concomitant use of*
- 57 *Thiazolidinediones (TZDs):* Observe for signs and symptoms of heart
- 58 failure; consider dosage reduction or discontinuation if heart failure occurs
- 59 (5.7).

60 -----ADVERSE REACTIONS-----
61 Adverse reactions commonly associated with RYZODEG 70/30 are:

- 62 • hypoglycemia, allergic reactions, injection site reactions, lipodystrophy,
- 63 pruritus, rash, edema and weight gain (6.1).

64 **To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk**
65 **at (1-800-727-6500) or FDA at 1-800-FDA-1088 or**
66 **www.fda.gov/medwatch.**

- 67 -----DRUG INTERACTIONS-----
- 68 • *Drugs that affect glucose metabolism:* Adjustment of insulin dosage may
 - 69 be needed; closely monitor blood glucose (7).
 - 70 • *Anti-Adrenergic Drugs (e.g., beta-blockers, clonidine, guanethidine, and*
 - 71 *reserpine):* Signs and symptoms of hypoglycemia may be reduced or
 - 72 absent (7).

73 **See 17 for PATIENT COUNSELING INFORMATION and FDA-**
74 **approved patient labeling.**

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131 **FULL PRESCRIBING INFORMATION**

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133 **1 INDICATIONS AND USAGE**

134 RYZODEG 70/30 is indicated to improve glycemic control in adults with diabetes mellitus.

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136 Limitations of Use

137 RYZODEG 70/30 is not recommended for the treatment of diabetic ketoacidosis

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139 **2 DOSAGE AND ADMINISTRATION**

140 **2.1 Important Administration Instructions**

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- 142 • Always check insulin label before administration [*see Warnings and Precautions(5.4)*].
- 143 • Inspect visually for particulate matter and discoloration. Only use RYZODEG 70/30 if
- 144 the solution appears clear and colorless.
- 145 • Train patients on proper use and injection technique before initiating RYZODEG 70/30.
- 146 Training reduces the risk of administration errors such as needle sticks and incomplete
- 147 dosing.
- 148 • Inject RYZODEG 70/30 subcutaneously into the thigh, upper arm, or abdomen.
- 149 • Rotate injection sites within the same region from one injection to the next to reduce the
- 150 risk of lipodystrophy [*see Adverse Reactions (6.1)*].
- 151 • DO NOT administer RYZODEG 70/30 intravenously, intramuscularly, or in an insulin
- 152 infusion pump.
- 153 • DO NOT dilute or mix RYZODEG 70/30 with any other insulin products or solutions.

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155 **2.2 General Dosing Instructions**

- 156 • Inject RYZODEG 70/30 subcutaneously once or twice daily with any main meal.
- 157 • Administer a rapid- or a short-acting insulin at other meals if needed.
- 158 • Patients with type 1 diabetes, will generally require a rapid- or short-acting insulin at
- 159 meals when RYZODEG 70/30 is not administered for optimal glucose control.
- 160 • Individualize and titrate the dose of RYZODEG 70/30 based on the patient's metabolic
- 161 needs, blood glucose monitoring results, and glycemic control goal [*see Warnings and*
- 162 *Precautions (5.2)*].
- 163 • Adjust the RYZODEG 70/30 dose according to blood glucose measurements before
- 164 breakfast (fasting).
- 165 • The recommended time between dose increases is 3 to 4 days.
- 166 • Dose adjustments may be needed with changes in physical activity, changes in meal
- 167 patterns (i.e., macronutrient content or timing of food intake), changes in renal or hepatic
- 168 function or during acute illness to minimize the risk of hypoglycemia or hyperglycemia
- 169 [*see Warnings and Precautions (5.3)*].
- 170 • If a dose of RYZODEG 70/30 is missed, the next dose should be taken with the next
- 171 main meal of that day and thereafter resume the usual dosing schedule. Patients should
- 172 not take an extra dose to make up for a missed dose.

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174 **2.3 Starting Dose in Insulin-Naïve Patients**

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176 *Type 1 Diabetes Mellitus*

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The recommended starting dose of RYZODEG 70/30 in insulin-naïve patients with type 1 diabetes is approximately one-third to one-half of the total daily insulin dose. The remainder of the total daily insulin dose should be administered as a short- or rapid-acting insulin divided between each daily meal. As a general rule, 0.2 to 0.4 units of insulin per kilogram of body weight can be used to calculate the initial total daily insulin dose in insulin-naïve patients with type 1 diabetes.

Type 2 Diabetes Mellitus

The recommended starting dose of RYZODEG 70/30 in insulin-naïve patients with type 2 diabetes mellitus is 10 units once daily.

2.4 Starting Dose in Patients with Type 1 or Type 2 Diabetes on a Once or Twice Daily Premix or Self-mix Insulin Alone or as Part of a Regimen of Multiple Daily Injections

- Start RYZODEG 70/30 at the same unit dose and injection schedule as the premix or self-mix insulin. In patients also using short- or rapid-acting insulin at mealtimes continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

2.5 Starting Dose in Patients with Type 1 or Type 2 Diabetes on a Once or Twice Daily Basal Insulin Alone or as Part of a Regimen of Multiple Daily Injections

- In patient with type 2 diabetes switching from a regimen that includes only a once- or twice-daily basal insulin, start RYZODEG 70/30 at the same unit dose and injection schedule. For patients switching from once-daily basal insulin to once-daily RYZODEG 70/30, monitor blood glucose after starting therapy due to the rapid-acting insulin component [*see Warnings and Precautions (5.2)*].
- In patients switching from a multiple daily injections regimen that includes a basal and short- or rapid-acting insulin at mealtimes, start RYZODEG 70/30 once daily with the main meal at the same unit dose as the basal insulin. Continue the short- or rapid-acting insulin at the same dose for meals NOT covered by RYZODEG 70/30.

3 DOSAGE FORMS AND STRENGTHS

RYZODEG 70/30 is available as a clear and colorless solution for injection in:

- 100 units/mL (U-100): 3 mL FlexTouch disposable prefilled pen

4 CONTRAINDICATIONS

RYZODEG 70/30 is contraindicated

- During episodes of hypoglycemia [*see Warnings and Precautions (5.3)*].
- In patients with hypersensitivity to RYZODEG 70/30 or one of its excipients [*see Warnings and Precautions (5.5)*].

223

224 5 WARNINGS AND PRECAUTIONS

225

226 5.1 Never Share a RYZODEG 70/30 FlexTouch Pen Between Patients

227 RYZODEG 70/30 FlexTouch disposable prefilled pen should never be shared between patients,
228 even if the needle is changed. Sharing poses a risk for transmission of blood-borne pathogens.

229

230 5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

231 Changes in insulin, manufacturer, type, or method of administration may affect glycemic control
232 and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously
233 and only under medical supervision and the frequency of blood glucose monitoring should be
234 increased. For patients with type 2 diabetes, adjustments in concomitant oral anti-diabetic
235 treatment may be needed. When converting from other insulin therapies to RYZODEG 70/30
236 follow dosing recommendations [see *Dosage and Administration (2.4, 2.5)*].

237

238 5.3 Hypoglycemia

239 Hypoglycemia is the most common adverse reaction of insulin, including RYZODEG 70/30 [see
240 *Adverse Reactions (6.1)*]. Severe hypoglycemia can cause seizures, may be life-threatening or
241 cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an
242 individual and others at risk in situations where these abilities are important (e.g., driving or
243 operating other machinery). RYZODEG 70/30, or any insulin, should not be used during
244 episodes of hypoglycemia [see *Contraindications (4)*].

245

246 Hypoglycemia can happen suddenly and symptoms may differ in each individual and change
247 over time in the same individual. Symptomatic awareness of hypoglycemia may be less
248 pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in
249 patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [see
250 *Drug Interactions (7)*], or in patients who experience recurrent hypoglycemia.

251

252 Risk Factors for Hypoglycemia

253 The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of
254 hypoglycemia after an injection is related to the duration of action of the insulin [see *Clinical*
255 *Pharmacology (12.2)*] and, in general, is highest when the glucose lowering effect of the insulin
256 is maximal. As with all insulin preparations, the glucose lowering effect time course of
257 RYZODEG 70/30 may vary in different individuals or at different times in the same individual
258 and depends on many conditions, including the area of injection as well as the injection site
259 blood supply and temperature.

260

261 Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g.,
262 macronutrient content or timing of meals), changes in level of physical activity, or changes to co-
263 administered medication [see *Drug Interactions (7)*]. Patients with renal or hepatic impairment
264 may be at higher risk of hypoglycemia [see *Use in Specific Populations (8.6, 8.7)*].

265

266 Risk Mitigation Strategies for Hypoglycemia

267 Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-
268 monitoring of blood glucose plays an essential role in the prevention and management of

269 hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced
270 symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is
271 recommended.

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273 **5.4 Hypoglycemia Due to Medication Errors**

274 Accidental mix-ups between insulin products have been reported. To avoid medication errors
275 between RYZODEG 70/30 and other insulins, instruct patients to always check the insulin label
276 before each injection.

277

278 Do not transfer RYZODEG 70/30 from the RYZODEG 70/30 pen to a syringe. The markings on
279 the insulin syringe will not measure the dose correctly and can result in overdosage and severe
280 hypoglycemia [*see Dosage and Administration (2.1) and Warnings and Precautions (5.3)*].

281

282 **5.5 Hypersensitivity and Allergic Reactions**

283 Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin
284 products, including RYZODEG 70/30. If hypersensitivity reactions occur, discontinue
285 RYZODEG 70/30; treat per standard of care and monitor until symptoms and signs resolve.
286 RYZODEG 70/30 is contraindicated in patients who have had hypersensitivity reactions to
287 insulin degludec, insulin aspart, or one of the excipients [*see Contraindications (4)*].

288

289 **5.6 Hypokalemia**

290 All insulin products, including RYZODEG 70/30, cause a shift in potassium from the
291 extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may
292 cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in
293 patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering
294 medications, patients taking medications sensitive to potassium concentrations).

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296 **5.7 Fluid Retention and Congestive Heart Failure with Concomitant Use of a PPAR 297 Gamma Agonist**

298 Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-
299 gamma agonists can cause dose related fluid retention, particularly when used in combination
300 with insulin. Fluid retention may lead to or exacerbate congestive heart failure. Patients treated
301 with insulin, including RYZODEG 70/30 and a PPAR-gamma agonist should be observed for
302 signs and symptoms of congestive heart failure. If congestive heart failure develops, it should be
303 managed according to current standards of care and discontinuation or dose reduction of the
304 PPAR-gamma agonist must be considered.

305

306 **6 ADVERSE REACTIONS**

307

308 The following adverse reactions are also discussed elsewhere:

- 309 • Hypoglycemia [*see Warnings and Precautions (5.3)*]
- 310 • Hypersensitivity and allergic reactions [*see Warnings and Precautions (5.5)*]
- 311 • Hypokalemia [*see Warnings and Precautions (5.6)*]

312

313 **6.1 Clinical Trial Experience**

314 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
315 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials
316 of another drug and may not reflect the rates observed in practice.

317

318 The safety of RYZODEG 70/30 in subjects with type 1 diabetes or type 2 diabetes was evaluated
319 in five treat-to-target trials of 6-12 month duration [see *Clinical Studies (14)*].

320

321 The data in Table 1 reflect the exposure of 362 patients with type 1 diabetes to RYZODEG
322 70/30, with a mean exposure duration to RYZODEG 70/30 of 43 weeks. The mean age was 41
323 years and 1% were older than 75 years. Fifty-two percent were male, 91% were White, 3% were
324 Black or African American and 3% were Hispanic. The mean body mass index (BMI) was 26
325 kg/m². The mean duration of diabetes was 17 years and the mean HbA_{1c} at baseline was 8.3%. A
326 history of neuropathy, ophthalmopathy, nephropathy and cardiovascular disease at baseline was
327 reported in 19%, 25%, 6% and 4% respectively. The mean eGFR at baseline was 88
328 mL/min/1.73 m² and 6% of patients had an eGFR less than 60 mL/min/1.73 m².

329

330 The data in Table 2 reflect the exposure of 998 patients with type 2 diabetes to RYZODEG 70/30
331 with a mean exposure duration to RYZODEG 70/30 of 24 weeks. The mean age was 58 years
332 and 3% were older than 75 years. Fifty-four percent were male, 44% were White, 4% were Black
333 or African American and 6% were Hispanic. The mean BMI was 29 kg/m². The mean duration
334 of diabetes was 12 years and the mean HbA_{1c} at baseline was 8.5%. A history of neuropathy,
335 ophthalmopathy, nephropathy and cardiovascular disease at baseline was reported for 15%, 21%,
336 10% and 1% respectively. At baseline, the mean eGFR was 84 mL/min/1.73 m² and 11% of
337 patients had an eGFR less than 60 mL/min/1.73 m².

338

339 Common adverse reactions (excluding hypoglycemia) occurring in RYZODEG 70/30-treated
340 subjects during clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes
341 mellitus are listed in Table 1 and Table 2, respectively. Common adverse reactions were defined
342 as reactions occurring in ≥5% of the population studied. Hypoglycemia is not shown in these
343 tables but discussed in a dedicated subsection below.

344

345 **Table 1: Adverse Reactions Occurring in ≥5% of RYZODEG 70/30-Treated Patients with**
346 **Type 1 Diabetes Mellitus**

347

Adverse Reaction	RYZODEG 70/30 (N=362)
Nasopharyngitis	24.6 %
Headache	9.7 %
Upper respiratory tract infection	9.1 %
Influenza	6.9 %

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350 **Table 2: Adverse Reactions Occurring in ≥5% of RYZODEG 70/30-Treated Patients with**
351 **Type 2 Diabetes Mellitus**

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Adverse Reaction	RYZODEG 70/30
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	(N=998)
Nasopharyngitis	11.1 %
Upper respiratory tract infection	5.7 %
Headache	5.6 %

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Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including RYZODEG 70/30 [see Warnings and Precautions (5.3)]. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for RYZODEG 70/30 with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that occur in clinical practice.

Rates of hypoglycemia by trial are shown in Table 3 for type 1 diabetes and Table 4 for type 2 diabetes for patients treated with RYZODEG 70/30 [see Clinical Studies (14)]. Severe hypoglycemia was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. A Novo Nordisk hypoglycemia episode was defined as a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

Table 3: Percent (%) of Patients with Type 1 Diabetes Experiencing at Least One Episode of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on RYZODEG 70/30 in Adult Clinical Trials

	Study A RYZODEG 70/30 OD* + INSULIN ASPART BID**, 52 weeks (N= 362)
Severe hypoglycemia	
Percent of patients	13.3%
Novo Nordisk hypoglycemia[§]	
Percent of patients	95.0%

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*OD: once daily
 **BID: twice daily
[§]Novo Nordisk hypoglycemia : a severe hypoglycemia episode or an episode where a laboratory or a self-measured glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with or without the presence of hypoglycemic symptoms).

384 **Table 4: Percent (%) of Patients with Type 2 Diabetes Experiencing at Least One Episode**
385 **of Severe Hypoglycemia or Novo Nordisk Hypoglycemia[§] on RYZODEG 70/30 in Adult**
386 **Clinical Trials**

	Study B RYZODEG 70/30 OD* insulin naïve, previously on 2 or more OADs*** (N=265)	Study C RYZODEG 70/30 OD* previously on basal insulin OD and 1 or more OADs*** (N=230)	Study D RYZODEG 70/30 BID** previously on OD*/BID premix/self-mix, ±OADs*** (N=224)	Study E RYZODEG 70/30 BID** previously on OD*/BID basal/premix/self-mix, ±OADs*** (N=279)
Severe hypoglycemia				
Percent of patients	0.4%	0%	3.1%	1.4%
Novo Nordisk hypoglycemia				
Percent of patients	49.8%	52.6%	66.1%	73.5%

387 *OD: once daily

388 **BID: twice daily

389 ***OAD: oral anti-diabetic agent

390 [§]Novo Nordisk hypoglycemia: a severe hypoglycemia episode or an episode where a laboratory or a self-measured
391 glucose calibrated to plasma was less than 56 mg/dL or where a whole blood glucose was less than 50 mg/dL (i.e., with
392 or without the presence of hypoglycemic symptoms).

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394 Allergic Reactions

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396 Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions,
397 angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including
398 RYZODEG 70/30 and may be life threatening [see *Warnings and Precautions (5.5)*].
399 Hypersensitivity (manifested with swelling of tongue and lips, diarrhea, nausea, tiredness and
400 itching) and urticaria were reported in 0.5% of patients treated with RYZODEG 70/30.

401

402 Lipodystrophy

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404 Long-term use of insulin, including RYZODEG 70/30, can cause lipodystrophy at the site of
405 repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose
406 tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate
407 insulin injection sites within the same region to reduce the risk of lipodystrophy [see *Dosage and*
408 *Administration (2.1)*]. In the clinical program, lipodystrophy was reported in 0.1% of patients
409 treated with RYZODEG 70/30.

410

411 Injection Site Reactions

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413 Patients taking RYZODEG 70/30 may experience injection site reactions, including injection site
414 hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritis, warmth, and
415 injection site mass. In the clinical program, injection site reactions occurred in 2.0% of patients
416 treated with RYZODEG 70/30.

417

418 Weight Gain

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420 Weight gain can occur with insulin therapy, including RYZODEG 70/30, and has been attributed
421 to the anabolic effects of insulin. In the clinical program, patients with type 1 diabetes treated
422 with RYZODEG 70/30 gained an average of 2.8 kg and patients with type 2 diabetes treated with
423 RYZODEG 70/30 gained an average of 1.6 kg.

424
425 Peripheral Edema

426
427 Insulin, including RYZODEG 70/30, may cause sodium retention and edema. In the clinical
428 program, peripheral edema, occurred in 2.2% of patients with type 1 diabetes mellitus and 1.8%
429 of patients with type 2 diabetes mellitus treated with RYZODEG 70/30.

430
431 **6.2 Immunogenicity**

432 As with all therapeutic proteins, insulin administration may cause anti-insulin antibodies to form.
433 The detection of antibody formation is highly dependent on the sensitivity and specificity of the
434 assay and may be influenced by several factors such as: assay methodology, sample handling,
435 timing of sample collection, concomitant medication, and underlying disease. For these reasons,
436 comparison of the incidence of antibodies to RYZODEG 70/30 with the incidence of antibodies
437 in other studies or to other products, may be misleading.

438
439 In studies of type 1 diabetes patients, 95.9% of patients who received RYZODEG 70/30 once
440 daily were positive for anti-insulin antibodies (AIA) at least once during the studies, including
441 89% that were positive at baseline, while 13% of these patients were positive for anti-IAsp
442 antibodies at least once during the studies, including 6.4% who were positive at baseline. In
443 studies of type 2 diabetes patients, 67.5% of patients who received RYZODEG 70/30 once daily
444 were positive for AIA at least once during the studies, including 45.4% that were positive at
445 baseline, while 17.1% of these patients were positive for anti-IAsp antibodies at least once
446 during the studies, including 12.3% who were positive at baseline. The antibody incidence rates
447 for type 2 diabetes may be underreported due to potential assay interference by endogenous
448 insulin in samples in these patients. The presence of antibodies that affect clinical efficacy may
449 necessitate dose adjustments to correct for tendencies toward hyper- or hypoglycemia.

450
451 The incidence of anti-insulin degludec antibodies has not been established.

452
453 **7 DRUG INTERACTIONS**

454
455 Table 5 includes clinically significant drug interactions with RYZODEG 70/30.

456
457 **Table 5: Clinically Significant Drug Interactions with RYZODEG 70/30**

Drugs That May Increase the Risk of Hypoglycemia	
<i>Drugs:</i>	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors.

<i>Intervention:</i>	Dose reductions and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of RYZODEG 70/30	
<i>Drugs:</i>	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.
<i>Intervention:</i>	Dose increases and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of RYZODEG 70/30	
<i>Drugs:</i>	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
<i>Intervention:</i>	Dose adjustment and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
<i>Drugs:</i>	Beta-blockers, clonidine, guanethidine, and reserpine.
<i>Intervention:</i>	Increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.

458

459

460 **8 USE IN SPECIFIC POPULATIONS**

461

462 **8.1 Pregnancy**

463 Pregnancy Category C

464

465 There are no adequate well-controlled clinical studies of the use of insulin degludec/insulin
 466 aspart in pregnant women. Patients should be advised to discuss with their health care provider if
 467 they intend to or if they become pregnant. Because animal reproduction studies are not always
 468 predictive of human response, insulin degludec/insulin aspart should be used during pregnancy
 469 only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with
 470 diabetes or a history of gestational diabetes to maintain good metabolic control before
 471 conception and throughout pregnancy. Insulin requirements may decrease during the first
 472 trimester, generally increase during the second and third trimesters, and rapidly decline after
 473 delivery. Careful monitoring of glucose control is essential in these patients.

474

475 An open-label, randomized study compared the safety and efficacy of NOVLOG (insulin
 476 aspart, the rapid-acting component of RYZODEG 70/30) versus human insulin in the treatment
 477 of pregnant women with Type 1 diabetes (322 exposed pregnancies (insulin aspart: 157, human
 478 insulin: 165). Two-thirds of the enrolled patients were already pregnant when they entered the

479 study. Since only one-third of the patients enrolled before conception, the study was not large
480 enough to evaluate the risk of congenital malformations. Mean HbA1c of ~ 6% was observed in
481 both groups during pregnancy, and there was no significant difference in the incidence of
482 maternal hypoglycemia.

483

484 Subcutaneous reproduction and teratology studies have been performed with insulin
485 degludec/insulin aspart, and human insulin (NPH) as a comparator in rats. In these studies,
486 insulin degludec/insulin aspart was given to rats during organogenesis. The effect of insulin
487 degludec/insulin aspart was consistent with those observed with human insulin as both caused
488 visceral/skeletal abnormalities in rats at dose of 30 U/kg/day (approximately 8 times the human
489 subcutaneous dose of 1.08 U/kg/day based on U/body surface area).

490

491 Subcutaneous reproduction and teratology studies have been performed with insulin degludec
492 (basal component of insulin degludec/insulin aspart), and human insulin (NPH) as a comparator
493 in rats and rabbits. In these studies, insulin was given to female rats before mating throughout
494 pregnancy until weaning, and to rabbits during organogenesis. The effect of insulin degludec was
495 consistent with those observed with human insulin as both caused pre- and post-implantation
496 losses and visceral/skeletal abnormalities in rats at an insulin degludec dose of 21 U/kg/day
497 (approximately 5 times the human exposure (AUC) at a human subcutaneous dose of 0.75
498 U/kg/day) and in rabbits at a dose of 3.3 U/kg/day (approximately 10 times the human exposure
499 (AUC) at a human subcutaneous dose of 0.75 U/kg/day). The effects are probably secondary to
500 maternal hypoglycemia.

501

502 Subcutaneous reproduction and teratology studies have been performed with NOVOLOG
503 (insulin aspart, the rapid-acting component of RYZODEG 70/30) and regular human insulin in
504 rats and rabbits. In these studies, insulin aspart was given to female rats before mating, during
505 mating, and throughout pregnancy, and to rabbits during organogenesis. The effects of insulin
506 aspart did not differ from those observed with subcutaneous regular human insulin. Insulin
507 aspart, like human insulin, caused pre- and post-implantation losses and visceral/skeletal
508 abnormalities in rats at a dose of 200 U/kg/day (approximately 32 times the human subcutaneous
509 dose of 1.0 U/kg/day, based on U/body surface area) and in rabbits at a dose of 10 U/kg/day
510 (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body
511 surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No
512 significant effects were observed in rats at a dose of 50 U/kg/day and in rabbits at a dose of 3
513 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day
514 for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits, based on U/body
515 surface area.

516

517 **8.3 Nursing Mothers**

518 It is unknown whether insulin degludec/aspart is excreted in human milk. Because many drugs,
519 including human insulin, are excreted in human milk, caution should be exercised when insulin
520 degludec/aspart is administered to a nursing mother. Women with diabetes who are lactating may
521 require adjustments in insulin dose, meal plan, or both.

522

523 In rats, the basal component of insulin degludec/aspart, insulin degludec, was secreted in milk
524 and the concentration in milk was lower than in plasma.

525

526 **8.4 Pediatric Use**

527 The safety and efficacy of RYZODEG 70/30 in children and adolescents under the age of 18
528 years have not been established.

529

530 **8.5 Geriatric Use**

531 In clinical studies [*see Clinical Studies (14)*] a total of 9 (2.5%) of the 362 RYZODEG 70/30-
532 treated patients with type 1 diabetes were 65 years or older and 4 (1.1%) were 75 years and
533 older. A total of 256 (25.7%) of the 998 RYZODEG 70/30-treated patients with type 2 diabetes
534 were 65 years or older and 32 (3.2%) were 75 years and older. Differences in safety or
535 effectiveness were not suggested in subgroup analyses comparing subjects older than 65 years to
536 younger subjects.

537

538 Nevertheless, greater caution should be exercised when RYZODEG 70/30 is administered to
539 geriatric patients since greater sensitivity of some older individuals to the effects of RYZODEG
540 70/30 cannot be ruled out. The initial dosing, dose increments, and maintenance dosage should
541 be conservative to avoid hypoglycemia. Hypoglycemia may be more difficult to recognize in the
542 elderly.

543

544 **8.6 Renal Impairment**

545 In clinical studies [*see Clinical Studies (14)*] a total of 18 (5%) of the 362 RYZODEG 70/30-
546 treated patients with type 1 diabetes had an eGFR less than 60 mL/min/1.73 m² or less and
547 1(0.3%) had an eGFR less than 30 mL/min/1.73 m² or less. A total of 111 (11%) of the 998
548 RYZODEG 70/30-treated patients with type 2 diabetes had an eGFR less than 60 mL/min/1.73
549 m² and no subjects had an eGFR less than 30 mL/min/1.73 m².

550

551 No differences in the pharmacokinetics of the individual components of RYZODEG 70/30,
552 insulin degludec or insulin aspart, were identified in separate studies comparing healthy subjects
553 and subjects with renal impairment [*see Clinical Pharmacology (12.3)*]. However, as with all
554 insulin products, glucose monitoring should be intensified and the RYZODEG 70/30 dosage
555 adjusted on an individual basis in patients with renal impairment.

556

557 **8.7 Hepatic Impairment**

558 No differences in the pharmacokinetics of the individual components of RYZODEG 70/30,
559 insulin degludec or insulin aspart, were identified in separate studies comparing healthy subjects
560 and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment) [*see*
561 *Clinical Pharmacology (12.3)*]. However, as with all insulin products, glucose monitoring should
562 be intensified and the RYZODEG 70/30 dosage adjusted on an individual basis in patients with
563 hepatic impairment.

564

565

566 **10 OVERDOSAGE**

567 An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and
568 sometimes prolonged and life-threatening hypoglycemia and hypokalemia [*see Warnings and*
569 *Precautions (5.3,5.6)*]. Mild episodes of hypoglycemia usually can be treated with oral glucose.
570 Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes of

571 hypoglycemia with coma, seizure, or neurologic impairment may be treated with
572 intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent
573 clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake
574 may be necessary to avoid reoccurrence of hypoglycemia. Hypokalemia must be corrected
575 appropriately.

576
577

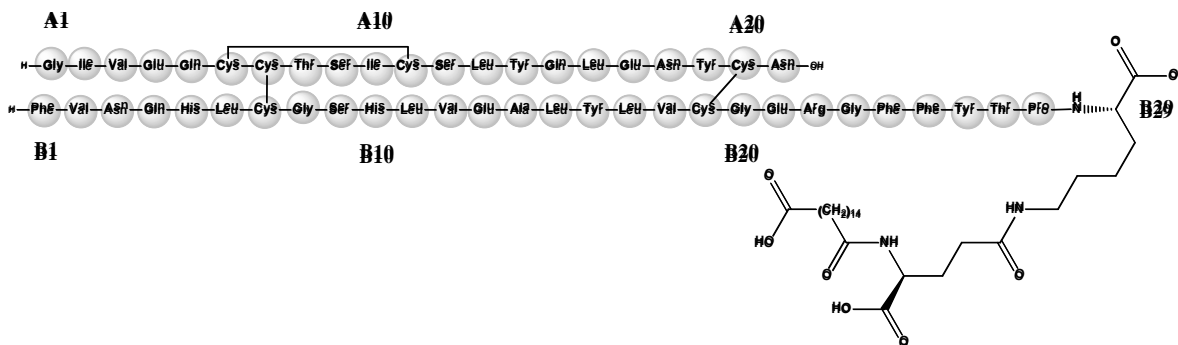
578 11 DESCRIPTION

579 RYZODEG 70/30 (insulin degludec and insulin aspart injection) is a human insulin analog
580 solution containing 70% insulin degludec and 30% insulin aspart for subcutaneous injection. It
581 consists of insulin degludec, a long-acting insulin, and insulin aspart, a rapid-acting insulin both
582 of which function as parenteral blood-glucose-lowering agents [see *Clinical Pharmacology*
583 (12)].

584

585 Insulin degludec differs from human insulin in that the amino acid threonine in position B30 has
586 been omitted and a side-chain consisting of glutamic acid and a C16 fatty acid has been attached
587 (chemical name: LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin) and is produced
588 by recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin degludec has a
589 molecular formula of C₂₇₄H₄₁₁N₆₅O₈₁S₆ and a molecular weight of 6103.97.

590
591

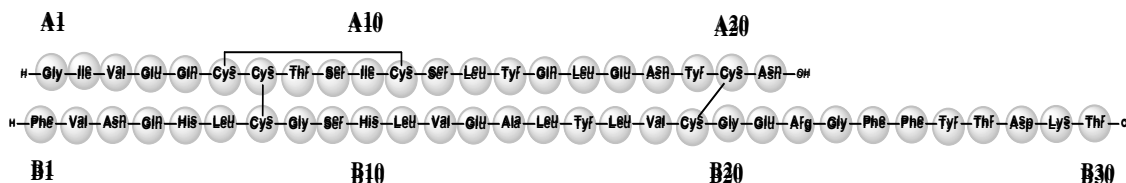


592
593

594 **Figure 1: Structural formula of insulin degludec**

595 Insulin aspart is homologous with regular human insulin with the exception of a single
596 substitution of the amino acid proline by aspartic acid in position B28, and is produced by
597 recombinant DNA technology utilizing *Saccharomyces cerevisiae*. Insulin aspart has a molecular
598 formula of C₂₅₆H₃₈₁N₆₅O₇₉S₆ and a molecular weight of 5825.8.

599



600
601

602 **Figure 2: Structural formula of insulin aspart**

603 RYZODEG 70/30 is a sterile, aqueous, clear, and colorless solution and contains a total of 100
604 Units of insulin degludec and insulin aspart mixture per mL, glycerol 19 mg/mL, metacresol 1.72
605 mg/mL, phenol 1.50 mg/mL, sodium chloride 0.58 mg/mL, zinc 27.4 mcg/mL and water for

606 injection. RYZODEG 70/30 has a pH of approximately 7.4. Hydrochloric acid or sodium
607 hydroxide may be added to adjust pH.

608

609 **12 CLINICAL PHARMACOLOGY**

610 **12.1 Mechanism of Action**

611 The primary activity of insulin, including RYZODEG 70/30, is regulation of glucose
612 metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose
613 uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production.
614 Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. The insulin
615 degludec component in RYZODEG 70/30 forms multi-hexamers when injected into the
616 subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The protracted time
617 action profile of RYZODEG 70/30 is predominantly due to delayed absorption of insulin
618 degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to
619 binding of insulin-degludec to circulating albumin. Insulin aspart monomers are released rapidly
620 into the circulation.

621

622 **12.2 Pharmacodynamics**

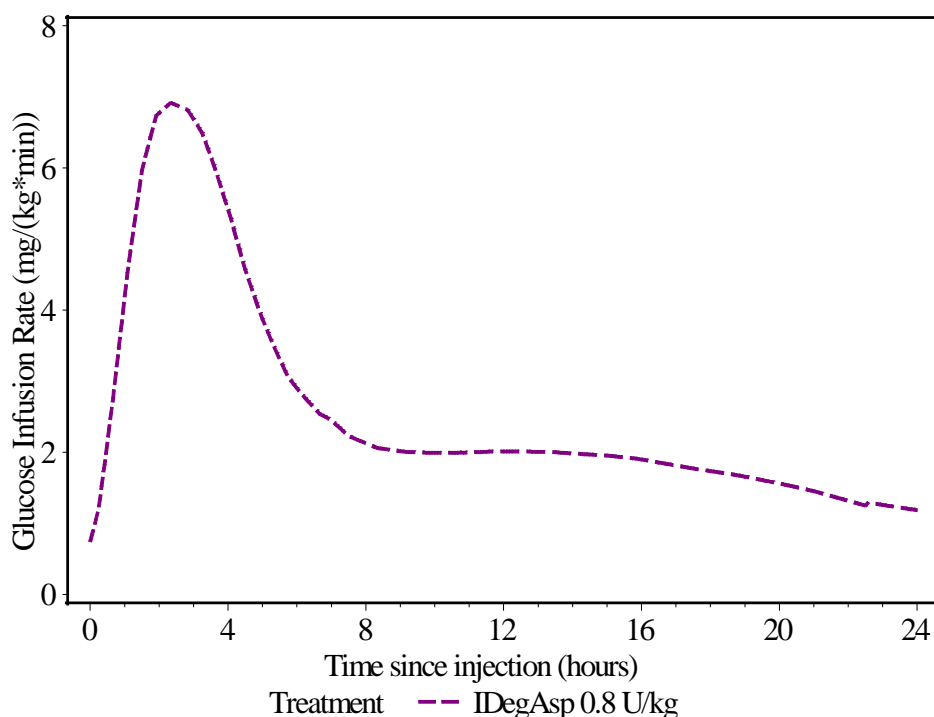
623 The pharmacodynamic profile of RYZODEG 70/30 reflects the action profiles of rapid-acting
624 insulin aspart and long-acting insulin degludec.

625

626 The pharmacodynamic profile for RYZODEG 70/30 given as single dose subcutaneous
627 injections of 0.8 U/kg dose in a euglycemic clamp study in patients with type 1 diabetes, is
628 shown in Figure 3. The mean maximum glucose lowering effect (GIR_{max}) of a 0.8 U/kg dose of
629 RYZODEG 70/30 was 6.9 mg/kg/min, which was observed at a median of 2.3 hours post-dose.

630 In patients with type 1 diabetes mellitus and type 2 diabetes mellitus, RYZODEG 70/30 has an
631 onset of action that rapidly follows injection. Basal insulin degludec in RYZODEG 70/30
632 provides a glucose lowering effect over 24 hours upon once-daily administration. The duration
633 of action of a single-dose of RYZODEG 70/30 may extend beyond 24 hours (Figure 3) due to
634 the presence of the basal component, insulin degludec.

635



636
637
638

639 **Figure 3: GIR profile of RYZODEG 70/30 after single 0.8 U/kg dose administration in**
640 **patients with type 1 diabetes mellitus**

641

642 The total and maximum glucose-lowering effect of RYZODEG 70/30 increases linearly with
643 increasing doses from 0.4U/kg to 0.8U/kg in patients with type 1 diabetes mellitus and type 2
644 diabetes mellitus. Steady state background glucose lowering, attributable to the long-acting,
645 insulin degludec component, will occur after 3 to 4 days of dose administration. However, the
646 magnitude of the glucose-lowering effect at steady state is reduced in type 2 diabetic subjects in
647 comparison to type 1 diabetic subjects given the same unit/kg RYZODEG 70/30 dose.

648

649 12.3 Pharmacokinetics

650

651 *Absorption*

652 The concentration-time profile following a single subcutaneous dose of 0.4, 0.6, and 0.8 U/kg
653 RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus showed
654 increased exposure with increasing dose for both components of RYZODEG 70/30 (insulin
655 degludec and insulin aspart).

656

657 Insulin aspart showed dose proportional increase in maximum concentration (C_{max}) and slightly
658 more than dose proportional increase in overall exposure AUC_{0-12h} following single
659 subcutaneous administration of RYZODEG 70/30 in patients with type 1 diabetes mellitus and
660 type 2 diabetes mellitus.

661

662 Insulin degludec showed dose proportional increase in C_{max} and AUC_{0-120h} following single
663 subcutaneous administration of RYZODEG 70/30 in patients with type 1 diabetes mellitus and
664 type 2 diabetes mellitus.

665

666 The median onset of appearance for the insulin aspart component was 14 minutes after injection
667 with a peak concentration after 72 minutes. Steady state serum concentrations of the insulin
668 degludec component of RYZODEG 70/30 were reached after 3 to 4 days of dose administrations
669 [see *Dosage and Administration* (2.2)].

670

671 *Distribution*

672 The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of
673 >99% in human plasma. Insulin aspart has low binding to plasma proteins, <10%, similar to
674 regular human insulin.

675

676 *Elimination*

677 The half-life after subcutaneous administration is determined primarily by the rate of absorption
678 from the subcutaneous tissue. The half-life of the basal component (insulin degludec) at steady
679 state is approximately 25 hours independent of dose. Degradation of insulin degludec is similar
680 to that of human insulin. All metabolites formed are inactive.

681

682 **Specific Populations**

683

684 As with other insulin preparations, RYZODEG 70/30 should always be titrated according to
685 individual requirements.

686

687 *Geriatrics-*

688 Pharmacokinetic and pharmacodynamic responses of RYZODEG 70/30 were investigated in 13
689 younger adult (18–35 years) and 15 geriatric (≥ 65 years) subjects with T1DM following two
690 single s.c. dose administrations of 0.5 U/kg: one of RYZODEG 70/30 and one of NovoLog Mix
691 70/30. The total exposure of insulin aspart in RYZODEG 70/30 (based on $AUC_{IAsp,0-12h,SD}$)
692 tended to be higher in geriatric subjects than in younger adult subjects. The total exposure of
693 insulin degludec in RYZODEG 70/30 (based on $AUC_{IDeg,0-120h,SD}$) and the pharmacodynamic
694 response to RYZODEG 70/30 (based on $AUC_{GIR,0-24h}$) was similar in younger adult and geriatric
695 subjects with T1DM, albeit higher between subjects variability among the geriatric subjects.

696

697 *Gender-*

698 The effect of gender on the pharmacokinetics of the separate components of RYZODEG 70/30,
699 insulin degludec and insulin aspart, was examined in across trial analyses of the pharmacokinetic
700 and pharmacodynamic studies. Overall, there were no clinically relevant differences in the
701 pharmacokinetic properties of insulin degludec or insulin aspart between female and male
702 subjects.

703

704 *Obesity-*

705 The effect of BMI on the pharmacokinetics of the separate components of RYZODEG 70/30,
706 insulin degludec and insulin aspart, was explored in cross-trial analyses of the pharmacokinetic
707 and pharmacodynamic studies. For subjects with type 1 diabetes, there was no relationship

708 between exposure of insulin degludec and BMI. For subjects with type 1 and type 2 diabetes, a
709 trend for decrease in glucose-lowering effect of insulin degludec with increasing BMI was
710 observed. For insulin aspart, there was no relationship between BMI and exposure in subjects
711 with T1DM or T2DM.

712

713 *Race and Ethnicity-*

714 The effect of race and ethnic origin on the pharmacokinetics of RYZODEG 70/30 has not been
715 studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a
716 pharmacokinetic and pharmacodynamic study in Black or African American subjects not of
717 Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White
718 subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus. There were no
719 statistically significant differences between the racial and ethnic groups investigated.

720

721 *Pregnancy-*

722 The effect of pregnancy on the pharmacokinetics and pharmacodynamics of RYZODEG 70/30
723 has not been studied [*see Use in Specific Populations (8.1)*].

724

725 *Renal Impairment-*

726 The effect of renal impairment on the pharmacokinetics of RYZODEG 70/30 has not been
727 studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a
728 pharmacokinetic study in 32 subjects (n=4-8/group) with normal or impaired renal function/end-
729 stage renal disease following administration of a single subcutaneous dose (0.4 U/kg) of insulin
730 degludec. Renal function was defined using creatinine clearance (Cl_{cr}) as follows: ≥ 90 mL/min
731 (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and < 30 mL/min (severe). Subjects
732 requiring dialysis were classified as having end-stage renal disease (ESRD). Total ($AUC_{IDeg,0-}$
733 $_{120h,SD}$) and peak exposure of insulin degludec were on average about 10-25% and 13-27%
734 higher, respectively in subjects with mild to severe renal impairment except subjects with ESRD
735 who showed similar exposure as compared to subjects with normal renal function. No systematic
736 trend was noted for this increase in exposure across different renal impairment subgroups.
737 Hemodialysis did not affect clearance of insulin degludec ($CL/F_{IDeg,SD}$) in subjects with ESRD.

738

739 A single subcutaneous dose of 0.08 U/kg NOVOLOG (insulin aspart, the rapid-acting
740 component of RYZODEG 70/30) was administered in a study to subjects with either normal,
741 mild, moderate or severe (but not requiring hemodialysis) renal impairment. In this study, there
742 was no apparent effect of creatinine clearance values on AUC and C_{max} of insulin aspart.

743

744 *Hepatic Impairment-*

745 The effect of hepatic impairment on the pharmacokinetics of RYZODEG 70/30 has not been
746 studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a
747 pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function
748 (mild, moderate, and severe hepatic impairment) following administration of a single
749 subcutaneous dose (0.4 U/kg) of insulin degludec. No differences in the pharmacokinetics of
750 insulin degludec were identified between healthy subjects and subjects with hepatic impairment
751 [*see Use in Specific Populations (8.7)*].

752

753 A single subcutaneous dose of 0.06 U/kg insulin aspart, the rapid-acting component of
754 RYZODEG 70/30, was administered in an open-label, single-dose study of 24 subjects
755 (n=6/group) with different degrees of hepatic impairment (mild, moderate, and severe). In this
756 study, there was no correlation between the degree of hepatic failure and any insulin aspart
757 pharmacokinetic parameter.

758

759

760 **13 NONCLINICAL TOXICOLOGY**

761 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

762 Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the
763 carcinogenic potential of insulin degludec/aspart RYZODEG 70/30.

764

765 In a 52-week study including human insulin (NPH insulin) as comparator, Sprague-Dawley rats
766 were dosed subcutaneously with insulin degludec, the basal component of insulin
767 degludec/aspart RYZODEG 70/30 at 3.3, 6.7, and 10 U/kg/day resulting in 5 times the human
768 exposure (AUC) when compared to a human subcutaneous dose of 1.08 U/kg/day RYZODEG
769 70/30. Human insulin was dosed at 6.7 U/kg/day. No treatment-related increases in incidences of
770 hyperplasia, benign or malignant tumors were recorded in female mammary glands from rats
771 dosed with insulin degludec and no treatment related changes in the female mammary gland cell
772 proliferation were found using BrdU incorporation. Further, no treatment related changes in the
773 occurrence of hyperplastic or neoplastic lesions were seen in other tissues in animals dosed with
774 insulin degludec when compared to vehicle or human insulin.

775

776 In 52-week studies, Sprague-Dawley rats were dosed subcutaneously with insulin aspart, the
777 rapid-acting component of insulin degludec/aspart RYZODEG 70/30, at 10, 50, and 200
778 U/kg/day (approximately 2, 8, and 32 times the human subcutaneous dose of 1.0 U/kg/day, based
779 on U/body surface area, respectively). At a dose of 200 U/kg/day, insulin aspart increased the
780 incidence of mammary gland tumors in females when compared to untreated controls. The
781 incidence of mammary tumors found with insulin aspart was not significantly different from that
782 found with regular human insulin. The relevance of these findings to humans is not known.

783

784 Genotoxicity testing of insulin degludec was not performed. Insulin aspart was not genotoxic in
785 the following tests: Ames test, mouse lymphoma cell forward gene mutation test, human
786 peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and
787 ex vivo UDS test in rat liver hepatocytes.

788

789 In a combined fertility and embryo-fetal study in male and female rats, treatment with insulin
790 degludec up to 21 U/kg/day (approximately 5 times the human subcutaneous dose of 0.75
791 U/kg/day, based on U/body surface area) prior to mating and in female rats during gestation had
792 no effect on mating performance.

793

794 In fertility studies with insulin aspart (NOVOLOG) in male and female rats, at subcutaneous
795 doses up to 200 U/kg/day (approximately 32 times the human subcutaneous dose, based on
796 U/body surface area), no direct adverse effects on male and female fertility, or general
797 reproductive performance of animals was observed.

798

799

800 **14 CLINICAL STUDIES**

801 The efficacy of RYZODEG 70/30 administered once-daily with the main meal of the day in
802 patients with type 1 diabetes and used with a mealtime insulin at remaining meals was evaluated
803 in one randomized, open-label, treat-to-target, active-controlled trial. The efficacy of RYZODEG
804 70/30 administered once or twice daily with the main meal(s) in patients with type 2 diabetes
805 when used with common oral anti-diabetic drugs was evaluated in four randomized, open-label,
806 treat-to-target, active controlled trials.

807

808 Patients treated with RYZODEG 70/30 achieved levels of glycemic control similar to those
809 treated with LANTUS (insulin glargine U-100) and LEVEMIR (insulin detemir) and
810 NOVOLOG MIX 70/30 (biphasic insulin aspart 70/30).

811

812 **14.1 Type 1 Diabetes – Adult**

813

814 *Study A: RYZODEG 70/30 Administered with the Main Meal in Combination with a Rapid-*
815 *Acting Insulin Analog at Remaining Meals*

816

817 The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label,
818 multicenter trial in 548 patients with type 1 diabetes mellitus inadequately controlled on either a
819 basal-bolus regimen or other insulin regimens at baseline. Patients were randomized to
820 RYZODEG 70/30 once-daily administered at the main meal of the day or insulin detemir once-
821 daily at the evening meal or at bedtime. Insulin aspart was administered for the remaining insulin
822 requiring meals. In patients randomized to detemir a second dose of insulin detemir could be
823 added at breakfast after 8 weeks if glycemic control was inadequate.

824

825 The mean age of the trial population was 41.3 years and mean duration of diabetes was 17.4
826 years. 49.6% were male. 90.3% were White, 2.9% Black or African American. 3.1% were
827 Hispanic. 4.8 % of patients had eGFR<60 mL/min/1.73m². The mean BMI was 26.4 kg/m².

828

829 At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and
830 insulin detemir was - 0.05% with a 95% confidence interval of (-0.18%, 0.08%) and met the pre-
831 specified non-inferiority margin (0.4%). See Table 6.

832

833 **Table 6: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin detemir in**
834 **Patients with type 1 diabetes mellitus receiving Insulin aspart at mealtimes**

	RYZODEG 70/30 + Insulin aspart	Insulin detemir* + Insulin aspart
N	366	182
HbA_{1c} (%)		
Baseline	8.3	8.3
End of trial	7.6	7.6
Adjusted mean change from baseline [±]	-0.75	-0.7
Estimated treatment	-0.05 [-0.18;0.08]	

difference [95%CI] RYZODEG 70/30 v. Insulin detemir		
Proportion Achieving HbA_{1c} < 7% at Trial End	24.6%	20.3%
FPG (mg/dL)		
Baseline	186	198
End of trial	156	155
Adjusted mean change from baseline	-29.7	-33.8
Total Daily insulin dose**		
Baseline mean	56 U	56 U
Mean dose after 26 weeks	69 U	79 U

835

*Dosed once-daily or twice daily

836

**Total daily insulin dose includes basal and bolus insulin doses

837

[‡]The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.

838

839

In Study A, there were 12.6% of subjects in RYZODEG 70/30 and 13.7% Insulin detemir arms for whom data was missing at the time of the HbA_{1c} measurement.

840

841

842

14.2 Type 2 Diabetes – Adult

843

844

Study B: RYZODEG 70/30 Administered with the Main Meal as an Add-on to Metformin in Insulin Naïve Patients

845

846

847

The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label, multicenter trial in 529 insulin-naïve patients with type 2 diabetes mellitus inadequately controlled on oral anti-diabetic drugs at baseline. Patients were randomized to RYZODEG 70/30 once-daily at breakfast or insulin glargine U-100 once-daily according to approved labeling. Metformin (Met) was administered in both arms.

849

850

851

852

853

The mean age of the trial population was 56.9 years and mean duration of diabetes was 9.2 years. 49.3% were male. 72.4% were White, 6.4% Black or African American. 21.6% were Hispanic. 4.5% of patients had eGFR<60 mL/min/1.73m². The mean BMI was 30.7 kg/m².

854

855

856

857

At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and insulin glargine U-100 was 0.03% with a 95% confidence interval of (-0.14%, 0.20%) and met the pre-specified non-inferiority margin (0.4%). See Table 7.

858

859

860

861

Table 7: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin glargine U-100 in Insulin-naïve Patients with type 2 diabetes mellitus

862

	RYZODEG 70/30 + Met	Insulin glargine U-100 + Met
N	266	263
HbA_{1c} (%)		

Baseline	8.9	8.9
End of trial	7.2	7.2
Adjusted mean change from baseline [±]	-1.72	-1.75
Estimated treatment difference [95% CI] RYZODEG 70/30 v. Insulin glargine U-100	0.03 [-0.14;0.20]	
Proportion Achieving HbA_{1c} < 7% at Trial End	45.9%	45.6%
FPG (mg/dL)		
Baseline	183	187
End of trial	123	114
Adjusted mean change from baseline	-63.3	-72.5
Post Prandial Glucose (mg/dL)		
Prandial increment at breakfast, baseline	61	65
Prandial increment at breakfast, end of trial	34	62
Adjusted mean change from baseline	-27.2	-2.0
Estimated treatment difference [95% CI] RYZODEG 70/30 v. Insulin glargine U-100	-25.2 [-34.5; -15.9] ¹	
Total Daily insulin dose		
Baseline mean	10 U	10 U
Mean dose after 26 weeks	66 U	59 U

863 ¹p<0.001, 1-sided p-value evaluated at 2.5% level for superiority

864 [±]The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex,
865 and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
866 In Study B, there were 17.7% of subjects in RYZODEG 70/30 and 12.9% Insulin glargine arms for whom data was
867 missing at the time of the HbA_{1c} measurement.

868

869

870 *Study C: RYZODEG 70/30 Administered with the Main Meal for Patients Inadequately*
871 *Controlled on Once-Daily Basal Insulin and Oral Agents*

872

873 The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label,
874 multicenter trial in 463 patients with type 2 diabetes mellitus inadequately controlled on basal
875 insulin once-daily and oral antidiabetic drugs at baseline. Patients were randomized to

876 RYZODEG 70/30 once-daily with either the evening meal or the largest meal of the day or
877 insulin glargine U-100 once-daily according to approved labeling. The starting intervention
878 insulin dose in units was determined by using the pre-trial basal insulin unit dose (1 to 1 unit
879 conversion). The same oral anti-diabetic drugs were continued in both treatment arms which
880 may have included any of the following used alone or in combination; Met, pioglitazone (Pio),
881 DPP-4 inhibitors (DPP-4i) throughout the entire trial.
882

883 The mean age of the trial population was 58.1 years and mean duration of diabetes was 11.5
884 years. 56.6% were male. 56.4% were White, 8.0% Black or African American. 4.5% were
885 Hispanic. 8.3% of patients had eGFR<60 mL/min/1.73m². The mean BMI was 30.1 kg/m².
886

887 At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and
888 insulin glargine U-100 was -0.03% with a 95% confidence interval of (-0.20%, 0.14%) and met
889 the pre-specified non-inferiority margin (0.4%). See Table 8.
890

891 **Table 8: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Insulin glargine U-**
892 **100 in Patients with type 2 diabetes mellitus**

	RYZODEG 70/30 + Met ± Pio ± DPP-4i	Insulin glargine U-100 + Met ± Pio ± DPP-4i
N	230	233
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.3	7.4
Adjusted mean change from baseline ±	-1.00	-0.97
Estimated treatment difference [95% CI] RYZODEG 70/30 v. Insulin glargine U-100	-0.03 [-0.20;0.14]	
Proportion Achieving HbA_{1c} < 7% at Trial End	40.0%	36.5%
FPG (mg/dL)		
Baseline	144	141
End of trial	114	108
Adjusted mean change from baseline	-28.9	-34.9
Post Prandial Glucose (mg/dL)		
Prandial increment at dinner, baseline	48	55
Prandial increment at dinner, end of trial	22	46
Adjusted mean change from baseline	-32.3	-8.3
Estimated treatment difference [95% CI] RYZODEG 70/30 v. Insulin	-23.9 [-34.7;-13.0] ¹	

glargine U-100		
Total Daily insulin dose		
Baseline mean	28 U	31 U
Mean dose after 26 weeks	60 U	60 U

893 p<0.001, 1-sided p-value evaluated at 2.5% level for superiority

894 [±]The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region, sex,
895 and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.

896 In Study C, there were 14.8 % of subjects in RYZODEG 70/30 and 12% Insulin glargine arms for whom data was
897 missing at the time of the HbA_{1c} measurement.

898 **Type 2 Diabetes – Adult, BID**

899

900 *Study D: RYZODEG 70/30 Administered with the Main Meal for Patients Inadequately*
901 *Controlled on Once-Daily or Twice-Daily Pre-Mix or Self-mixed Insulin*

902

903 The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label,
904 multicenter trial in 446 patients with type 2 diabetes mellitus inadequately controlled on once or
905 twice daily premixed or self-mixed insulin with or without background oral anti-diabetic agents.
906 Patients were randomized to RYZODEG 70/30 or biphasic insulin aspart 70/30, both
907 administered twice daily before the breakfast and main evening meals. Subjects on premixed
908 insulin twice daily initiated trial insulin at the same dose as their premixed insulin (1 to 1 unit
909 conversion). Subjects on a self-mixed regimen transfer to trial insulin at doses corresponding to
910 their respective self-mixed pre-meal dose. Subjects previously receiving premixed or self-mixed
911 insulin once-daily were to divide their dose into 2 equal doses. Patients continued on pre-trial
912 oral background therapies which may have included any of the following used alone or in
913 combination; Met, Pio, DPP-4i throughout the entire trial.

914

915 The mean age of the trial population was 58.7 years and mean duration of diabetes was 13.0
916 years. 55.6% were male. 52.5% were White, 0.2% Black or African American. 0.4% were
917 Hispanic. 14.3% of patients had eGFR<60 mL/min/1.73m². The mean BMI was 29.3 kg/m².

918

919 At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and
920 biphasic insulin aspart 70/30 was -0.03% with a 95% confidence interval of (-0.18%, 0.13%) and
921 met the pre-specified non-inferiority margin (0.4%). See Table 9.

922 **Table 9: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Biphasic insulin**
923 **aspart 70/30 in Patients with type 2 diabetes mellitus**

	RYZODEG 70/30 ± Met ± Pio ± DPP-4i	Biphasic insulin aspart 70/30 ± Met ± Pio ± DPP-4i
N	224	222
HbA_{1c} (%)		
Baseline	8.3	8.4
End of trial	7.1	7.1
Adjusted mean change from baseline [±]	-1.31	-1.29

Estimated treatment difference [95% CI] RYZODEG 70/30 v. Biphasic insulin aspart 70/30	-0.03 [-0.18;0.13]	
Proportion Achieving HbA_{1c} < 7% at Trial End	50.4%	48.6%
FPG (mg/dL)		
Baseline	160	155
End of trial	104	123
Adjusted mean change from baseline	-50.4	-29.8
Total Daily insulin dose		
Baseline mean	54 U	51 U
Mean dose after 26 weeks	90 U	98 U

924 [±] The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region,
925 sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
926 In Study D, there were 12.1 % of subjects in RYZODEG 70/30 and 15.3% Biphasic insulin aspart 70/30 arms for
927 whom data was missing at the time of the HbA_{1c} measurement.

928

929 *Study E : RYZODEG 70/30 Administered with Any Main Meal for Patients Inadequately*
930 *Controlled on Basal Insulin, Pre-Mix or Self-mixed Insulin*

931

932 The efficacy of RYZODEG 70/30 was evaluated in a 26-week randomized, open-label,
933 multicenter trial in 422 patients with type 2 diabetes mellitus inadequately controlled on basal
934 insulin, premixed or self-mixed insulin in a once or twice daily insulin with or without
935 background Met. Patients were randomized to RYZODEG 70/30 or biphasic insulin aspart
936 70/30, both administered twice daily at the breakfast and main evening meal. Subjects on once-
937 daily insulin split the total dose of their previous insulin treatment into 2 equal doses of trial
938 insulin for twice daily administration. Subjects on twice daily insulin transferred their doses on a
939 unit-to-unit basis to the trial insulin. Patients on Met continued Met at their pre-trial dose.

940

941 The mean age of the trial population was 59.8 years and mean duration of diabetes was 16.3
942 years. 54.5% were male. All patients were Asian. 17.2% of patients had eGFR<60
943 mL/min/1.73m². The mean BMI was approximately 25.4 kg/m².

944

945 At week 26, the difference in HbA_{1c} reduction from baseline between RYZODEG 70/30 and
946 biphasic insulin aspart 70/30 was 0.05% with a 95% confidence interval of (-0.10%, 0.20%) and
947 met the pre-specified non-inferiority margin (0.4%). See Table 10.

948

949 **Table 10: Results at Week 26 in a Trial Comparing RYZODEG 70/30 to Biphasic insulin**
950 **aspart 70/30 in Asian Patients with type 2 diabetes mellitus**

	RYZODEG 70/30 ± Met	Biphasic insulin aspart 70/30 ± Met
N	280	142

HbA_{1c} (%)		
Baseline	8.4	8.4
End of trial	7.1	7.0
Adjusted mean change from baseline [±]	-1.39	-1.44
Estimated treatment difference [95% CI] RYZODEG 70/30 v. Biphasic insulin aspart 70/30	0.05 [-0.10;0.20]	
Proportion Achieving HbA_{1c} < 7% at Trial End	48.2%	49.3%
FPG (mg/dL)		
Baseline	143	143
End of trial	97	116
Adjusted mean change from baseline	-45.3	-26.2
Total Daily insulin dose		
Baseline mean	37 U	37 U
Mean dose after 26 weeks	55 U	68 U

951 [±] The change from baseline to end of treatment visit in HbA_{1c} was analysed using ANOVA with treatment, region,
952 sex, and anti-diabetic treatment at screening as fixed effects, and age and baseline HbA_{1c} as covariates.
953 In Study E, there were 12.1 % of subjects in RYZODEG 70/30 and 10.6% Biphasic insulin aspart 70/30 arms for
954 whom data was missing at the time of the HbA_{1c} measurement.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

956 RYZODEG 70/30 is as a clear, and colorless solution available as a 3mL FlexTouch disposable
957 prefilled pen (see Table 11).
958
959
960

961 **Table 11 Presentations of RYZODEG 70/30**

RYZODEG 70/30	Total volume	Concentration	Total units available in presentation	NDC number	Max dose per injection	Dose increment	Package Size
U-100 FlexTouch	3 mL	100 units/mL	300 Units	0169-2770-15	80 Units	1 Unit	5 pens/

16.2 Recommended Storage

962 Unused RYZODEG 70/30 should be stored between 36° to 46°F (2° and 8°C). Do not store
963 in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze. Do not use
964 RYZODEG 70/30 if it has been frozen.
965
966
967

968 Unopened FlexTouch disposable prefilled pen:
969 Not in-use (unopened) RYZODEG 70/30 disposable prefilled pen should be stored in a
970 refrigerator 36° to 46°F (2° and 8°C). Discard after expiration date.

971
972 Open (In-Use) FlexTouch disposable prefilled pen:
973 The in-use RYZODEG 70/30 FlexTouch pen should NOT be refrigerated but should be kept at
974 room temperature, below 30°C (86°F) away from direct heat and light. The opened (in-use)
975 RYZODEG 70/30 FlexTouch pen may be used for up to 28 days (4 weeks) after being opened, if
976 it is kept at room temperature.

977
978 The storage conditions are summarized in Table 12:
979

980 **Table 12: Storage Conditions for RYZODEG 70/30 FlexTouch**

	Not in-use (unopened) Refrigerated (36°F - 46°F [2°C - 8°C])	Not in-use (unopened) Room Temperature (below 86°F [30°C])	In-use (opened) Room Temperature (below 86°F [30°C])
3 mL RYZODEG 70/30 U100 FlexTouch	Until expiration date	28 days (4 weeks)	28 days (4 weeks) (Do not refrigerate)

981

982 **17 PATIENT COUNSELING INFORMATION**

983 See FDA-Approved Patient Labeling (Patient Information and Instructions for Use)

984

985 **Never Share a RYZODEG 70/30 FlexTouch Pen Device Between Patients**

986 Advise patients that they should never share a RYZODEG 70/30 FlexTouch pen device with
987 another person, even if the needle is changed, because doing so carries a risk for transmission of
988 blood-borne pathogens [see *Warnings and Precautions (5.1)*].

989

990 **Hyperglycemia or Hypoglycemia**

991 Inform patients that hypoglycemia is the most common adverse reaction with insulin. Inform
992 patients of the symptoms of hypoglycemia. Inform patients that the ability to concentrate and
993 react may be impaired as a result of hypoglycemia. This may present a risk in situations where
994 these abilities are especially important, such as driving or operating other machinery. Advise
995 patients who have frequent hypoglycemia or reduced or absent warning signs of hypoglycemia to
996 use caution when driving or operating machinery.

997

998 Advise patients that changes in insulin regimen can predispose to hyper- or hypoglycemia.

999 Advise patients that changes in insulin regimen should be made under close medical supervision
1000 [see *Warnings and Precautions (5.2)*].

1001

1002 **Medication errors**

1003 Inform patients to always check the insulin label before each injection [see *Warnings and*
1004 *Precautions (5.4)*].

1005

1006 Instruct patients that when injecting RYZODEG 70/30, they must press and hold down the dose
1007 button until the dose counter shows 0 and then keep the needle in the skin and count slowly to 6.
1008 When the dose counter returns to 0, the prescribed dose is not completely delivered until 6
1009 seconds later. If the needle is removed earlier, they may see a stream of insulin coming from the
1010 needle tip. If so, the full dose will not be delivered, (a possible under-dose may occur by as much
1011 as 20%), and they should increase the frequency of checking their blood glucose levels and
1012 possible additional insulin administration may be necessary.

- 1013 • If 0 does not appear in the dose counter after continuously pressing the dose button, the
1014 patient may have used a blocked needle. In this case they would **not** have received **any**
1015 insulin—even though the dose counter has moved from the original dose that was set.
- 1016 • If the patient did have a blocked or damaged needle, instruct them to change the needle as
1017 described in Step 15 of the Instructions for Use and repeat all steps in the IFU starting
1018 with a new needle and the section Preparing your RYZODEG 70/30 FlexTouch Pen.
1019 **Make sure the patient selects the full dose needed.**

1020
1021 If patients routinely do not hold the needle under the skin as recommended, the patient may need
1022 to slightly increase the dialed insulin dose to achieve the patient’s glycemic targets.

1023
1024 Instruct patients to not re-use needles. A new needle must be attached before each injection.
1025 Reuse of needles increases the risk of blocked needles which may cause under-dosing or
1026 overdosing.

1027
1028 Instruct Patients to never use a syringe to remove RYZODEG 70/30 from the FlexTouch
1029 disposable insulin prefilled pen.

1030 1031 **Administration**

1032 RYZODEG 70/30 must only be used if the solution is clear and colorless with no particles
1033 visible.

1034 Patients must be advised that RYZODEG 70/30 must NOT be diluted or mixed with any other
1035 insulin or solution [see *Dosage and Administration (2.1)*].

1036 1037 **Management of Hypoglycemia and Handling of Special Situations**

1038 Patients should be instructed on self-management procedures including glucose monitoring,
1039 proper injection technique, and management of hypoglycemia and hyperglycemia. Patients must
1040 be instructed on handling of special situations such as intercurrent conditions (illness, stress, or
1041 emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an
1042 increased insulin dose, inadequate food intake, and skipped meals [see *Warnings and*
1043 *Precautions (5.3)*].

1044
1045 Refer patients to the RYZODEG 70/30 “Patient Information” for additional information about
1046 the potential side effects of insulin therapy, including lipodystrophy (and the need to rotate
1047 injection sites within the same body region), weight gain, allergic reactions, and hypoglycemia.

1048 1049 **Women of Reproductive Potential**

1050 Advise patients to inform their health care professional if they are pregnant or are contemplating
1051 pregnancy.

1052

1053

1054 **Rx Only**

1055

1056 Date of Issue:

1057 Version:

1058

1059 *Novo Nordisk*[®], *RYZODEG 70/30*[®], *FlexTouch*[®], *Levemir*[®], *NovoLog*[®], *NovoFine*[®], and
1060 *NovoTwist*[®] are registered trademarks of Novo Nordisk A/S.

1061

1062 © 201X Novo Nordisk

1063

1064 RYZODEG[®] 70/30 is covered by US Patent Nos. 5,866,538, 7,615,532 and other patents
1065 pending.

1066 FlexTouch[®] is covered by US Patent Nos. 6,899,699, 7,686,786, 8,672,898, 8,684,969,
1067 8,920,383, D724,721, D734,450 and other patents pending.

1068

1069 Manufactured by:

1070 Novo Nordisk A/S

1071 DK-2880 Bagsvaerd, Denmark

1072

1073 For information about RYZODEG 70/30 contact:

1074 Novo Nordisk Inc.

1075 800 Scudders Mill Road

1076 Plainsboro, NJ 08536

1077

1078 1-800-727-6500

1079

1080 www.novonordisk-us.com

1081

Patient Information
RYZODEG[®] 70/30 (RY-zoh-deg)
(insulin degludec and insulin aspart injection)

Do not share your RYZODEG 70/30 FlexTouch delivery device with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them.

What is RYZODEG 70/30?

- RYZODEG 70/30 is a man-made insulin that is used to control high blood sugar in adults with diabetes mellitus.
- RYZODEG 70/30 is not for people with diabetic ketoacidosis (increased ketones in the blood or urine).
- It is not known if RYZODEG 70/30 is safe and effective in children under 18 years of age.

Who should not take RYZODEG 70/30?

Do not take RYZODEG 70/30 if you:

- are having an episode of low blood sugar (hypoglycemia).
- have an allergy to RYZODEG 70/30 or any of the ingredients in RYZODEG 70/30.

Before taking RYZODEG 70/30, tell your healthcare provider about all your medical conditions including, if you are:

- pregnant, planning to become pregnant, or are breastfeeding.
- taking new prescription or over-the-counter medicines, vitamins, or herbal supplements.

Before you start taking RYZODEG 70/30, talk to your healthcare provider about low blood sugar and how to manage it.

How should I take RYZODEG 70/30?

- **Read the Instructions for Use** that come with your RYZODEG 70/30.
- Take RYZODEG 70/30 exactly as your healthcare provider tells you to.
- **RYZODEG 70/30 starts acting fast.** Inject RYZODEG 70/30 with your meal.
- If you take RYZODEG 70/30 1 time each day, take your dose with any main meal. If you take RYZODEG 70/30 2 times each day, take your dose with your 2 largest meals.
- Know the type and strength of insulin you take. **Do not** change the type of insulin you take unless your healthcare provider tells you to. The amount of insulin and the best time for you to take your insulin may need to change if you take different types of insulin.
- If you miss or are delayed in taking a dose of RYZODEG 70/30:
 - Take your next dose with your next main meal on the same day and continue with your regular dosing schedule.
 - **Do not** take an extra dose.
- **Check your blood sugar levels.** Ask your healthcare provider what your blood sugars should be and when you should check your blood sugar levels.
- **Do not reuse or share needles with other people. You may give other people a serious infection or get a serious infection from them.**
- **Never** inject RYZODEG 70/30 into a vein or muscle.
- **Never** use a syringe to remove RYZODEG 70/30 from the FlexTouch pen.

What should I avoid while taking RYZODEG 70/30?

While taking RYZODEG 70/30 do not:

- Drive or operate heavy machinery, until you know how RYZODEG 70/30 affects you.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

What are the possible side effects of RYZODEG 70/30?

RYZODEG 70/30 may cause serious side effects that can lead to death, including:

- **Low blood sugar (hypoglycemia).** Signs and symptoms that may indicate low blood sugar include:
 - dizziness or light-headedness
 - blurred vision
 - anxiety, irritability, or mood changes
 - sweating
 - slurred speech
 - hunger
 - confusion
 - shakiness
 - headache
 - fast heart beat
- **Low potassium in your blood (hypokalemia).**
- **Heart failure.** Taking certain diabetes pills called thiazolidinediones or “TZDs” with RYZODEG 70/30 may cause heart failure in some people. This can happen even if you have never had heart failure or heart problems before. If you already have heart failure, it may get worse while you take TZDs with RYZODEG 70/30. Your healthcare provider should monitor you closely while you are taking TZDs with RYZODEG 70/30. Tell your healthcare provider if you have any new or worse symptoms of heart failure including shortness of breath, swelling of your ankles or feet, tiredness, sudden weight gain. Treatment with TZDs and RYZODEG 70/30 may need to be adjusted or stopped by your healthcare provider if you have new or worse heart failure.

Your insulin dose may need to change because of:

- change in level of physical activity or exercise
- increased stress
- change in diet
- weight gain or loss
- illness

Common side effects of RYZODEG 70/30 may include:

- serious allergic reactions (whole body reactions), reactions at the injection site, skin thickening or pits at the injection site (lipodystrophy), itching, rash, swelling of your hands and feet, and weight gain.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, swelling of your face, tongue, or throat, sweating, extreme drowsiness, dizziness, confusion.

These are not all the possible side effects of RYZODEG 70/30. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of RYZODEG 70/30.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about RYZODEG 70/30 that is written for health professionals. Do not use RYZODEG 70/30 for a condition for which it was not prescribed. Do not give RYZODEG 70/30 to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in RYZODEG 70/30?

Active Ingredient: 70% insulin degludec and 30% insulin aspart

Inactive Ingredients: zinc, metacresol, glycerol, phenol, sodium chloride, and water for injection. Hydrochloric acid or sodium hydroxide may be added.

Manufactured by:

Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

For more information, go to www.novonordisk-us.com or call 1-800-727-6500.

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: 09/2015

Instructions for Use

RYZODEG[®] 70/30 (RY-zoh-deg) FlexTouch[®] Pen 100 units/mL

(insulin degludec and insulin aspart injection)

- **Do not share your RYZODEG 70/30 FlexTouch Pen with other people, even if the needle is changed. You may give other people a serious infection, or get a serious infection from them.**
- **RYZODEG 70/30 FlexTouch Pen 100 units/mL (“Pen”) is a prefilled disposable pen** containing 300 units of RYZODEG 70/30 (insulin degludec and insulin aspart injection) 100 units/mL insulin. You can inject from 1 to 80 units in a single injection. The units can be increased by 1 unit at a time.
- **This Pen is not recommended for use by the blind or visually impaired without the assistance of a person trained in the proper use of the product.**

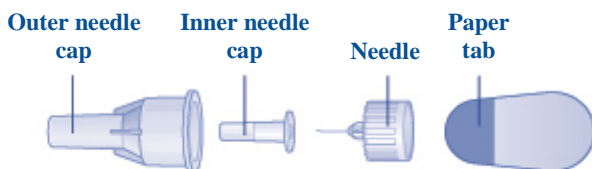
Supplies you will need to give your RYZODEG 70/30 injection:

- RYZODEG 70/30 FlexTouch Pen
- a new NovoFine or NovoTwist needle
- alcohol swab
- a sharps container for throwing away used Pens and needles. **See “After your injection” at the end of these instructions.**

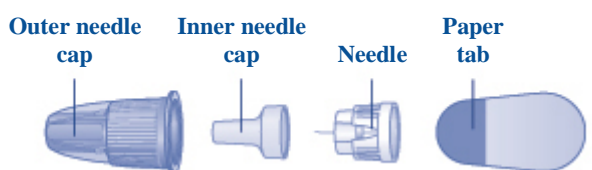
Preparing your RYZODEG 70/30 FlexTouch Pen:

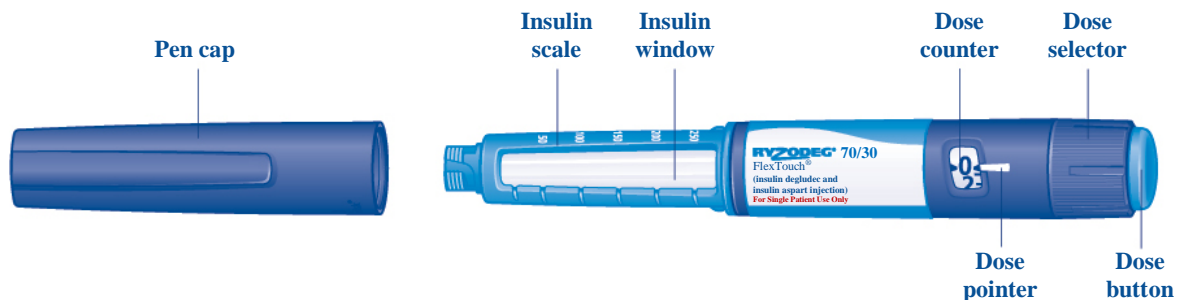
- Wash your hands with soap and water.
- **Before you start to prepare your injection, check the RYZODEG 70/30 FlexTouch Pen label to make sure you are taking the right type of insulin. This is especially important if you take more than 1 type of insulin.**
- RYZODEG 70/30 should look clear and colorless. **Do not** use RYZODEG 70/30 if it is cloudy or colored.
- **Do not** use RYZODEG 70/30 past the expiration date printed on the label or 28 days after you start using the Pen.
- **Always use a new needle for each injection to help ensure sterility and prevent blocked needles. Do not reuse or share needles with another person. You may give other people a serious infection, or get a serious infection from them.**

NovoFine[®]



NovoTwist[®]

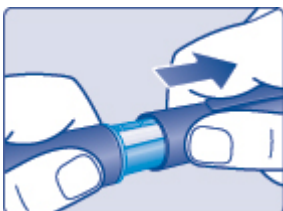




(Figure A)

Step 1:

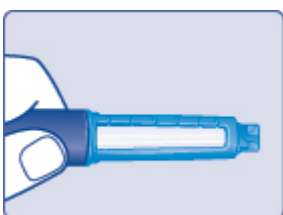
- Pull Pen cap straight off (See Figure B).



(Figure B)

Step 2:

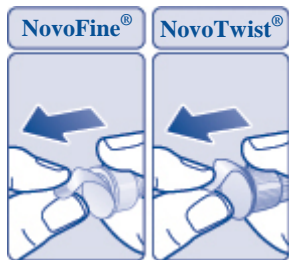
- **Check the liquid in the Pen** (See Figure C). RYZODEG 70/30 should look clear and colorless.
Do not use it if it looks cloudy or colored.



(Figure C)

Step 3:

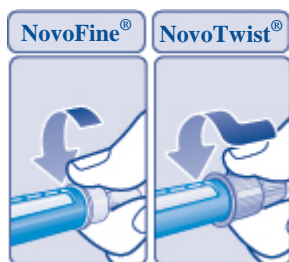
- **Select a new needle.**
- Pull off the paper tab from the outer needle cap (See Figure D).



(Figure D)

Step 4:

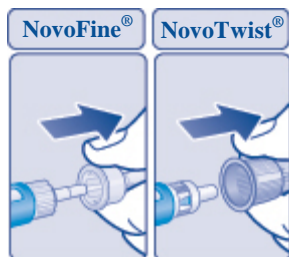
- Push the capped needle straight onto the Pen and twist the needle on until it is tight (See Figure E).



(Figure E)

Step 5:

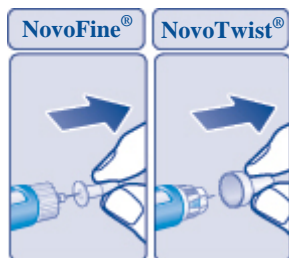
- Pull off the outer needle cap. **Do not** throw it away (See Figure F).



(Figure F)

Step 6:

- Pull off the inner needle cap and throw it away (See Figure G).



(Figure G)

Priming your RYZODEG 70/30 FlexTouch Pen:

Step 7:

- Turn the dose selector to **select 2 units** (See Figure H).



(Figure H)

Step 8:

- **Hold the Pen with the needle pointing up.** Tap the top of the Pen gently a few times to let any air bubbles rise to the top (See Figure I).



(Figure I)

Step 9:

- **Hold the Pen with the needle pointing up.** Press and hold in the dose button until the dose counter shows "0". The "0" must line up with the dose pointer.
- A drop of insulin should be seen at the needle tip (See Figure J).
 - o If you **do not** see a drop of insulin, repeat steps 7 to 9, no more than 6 times.
 - o If you **still do not** see a drop of insulin, change the needle and repeat steps 7 to 9.



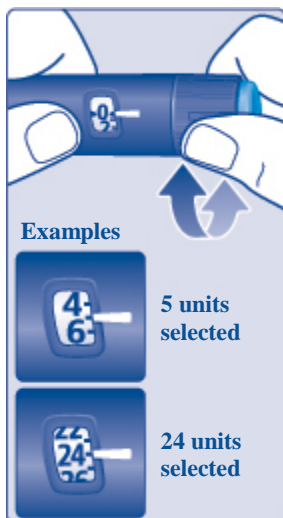
(Figure J)

Selecting your dose:

Step 10:

Check to make sure the dose selector is set at 0.

- **Turn the dose selector to select the number of units you need to inject.** The dose pointer should line up with your dose (See Figure K).
 - o If you select the wrong dose, you can turn the dose selector forwards or backwards to the correct dose.
 - o The **even** numbers are printed on the dial.
 - o The **odd** numbers are shown as lines.



(Figure K)

- The RYZODEG 70/30 FlexTouch Pen insulin scale will show you how much insulin is left in your Pen (See Figure L).



(Figure L)

- **To see how much insulin is left in your RYZODEG 70/30 FlexTouch Pen:**

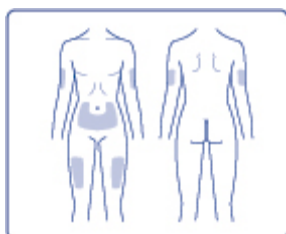
- o Turn the dose selector until it stops. The dose counter will line up with the number of units of insulin that is left in your Pen. If the dose counter shows 80, there are **at least 80** units left in your Pen.
- o If the dose counter shows **less than 80**, the number shown in the dose counter is the number of units left in your Pen.

Giving your injection:

- Inject your RYZODEG 70/30 exactly as your healthcare provider has shown you. Your healthcare provider should tell you if you need to pinch the skin before injecting.
- RYZODEG 70/30 can be injected under the skin (subcutaneously) of your upper legs (thighs), upper arms, or stomach area (abdomen).
- Change (rotate) your injection sites within the area you choose for each dose. **Do not** use the same injection site for each injection.

Step 11:

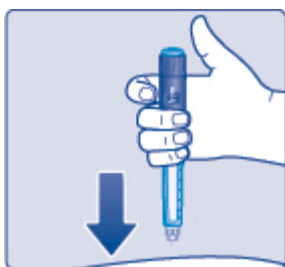
- Choose your injection site and wipe the skin with an alcohol swab (See Figure M). Let the injection site dry before you inject your dose.



(Figure M)

Step 12:

- **Insert the needle into your skin** (See Figure N).
 - **Make sure you can see the dose counter. Do not** cover it with your fingers, this can stop your injection.



(Figure N)

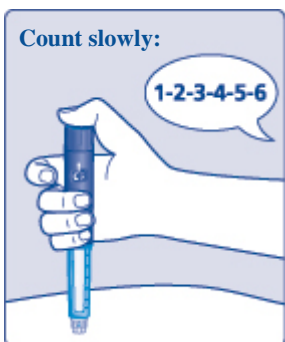
Step 13:

- **Press and hold down the dose button until the dose counter shows “0”** (See Figure O).
 - The “0” must line up with the dose pointer. You may then hear or feel a click.



(Figure O)

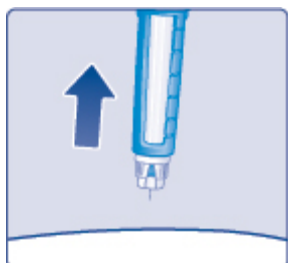
- **Keep the needle in your skin after** the dose counter has returned to “0” and **slowly count to 6** (See Figure P).
 - **When the dose counter returns to “0”, you will not get your full dose until 6 seconds later.**
 - **If the needle is removed before you count to 6, you may see a stream of insulin coming from the needle tip.**
 - **If you see a stream of insulin coming from the needle tip you will not get your full dose. If this happens you should check your blood sugar levels more often because you may need more insulin.**



(Figure P)

Step 14:

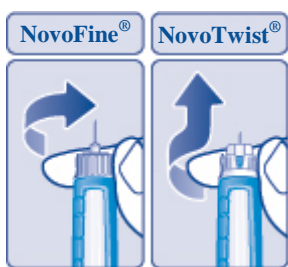
- **Pull the needle out of your skin** (See Figure Q).
 - o If you see blood after you take the needle out of your skin, press the injection site lightly with a piece of gauze or an alcohol swab. **Do not** rub the area.



(Figure Q)

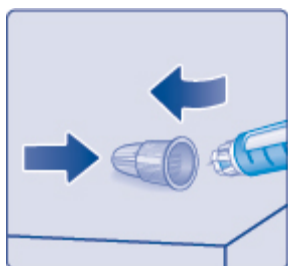
Step 15:

- **Carefully remove the needle from the Pen and throw it away** (See Figure R).
 - o **Do not** recap the needle. Recapping the needle can lead to needle stick injury.



(Figure R)

- If you **do not** have a sharps container, carefully slip the needle into the outer needle cap (See Figure S). Safely remove the needle and throw it away as soon as you can.

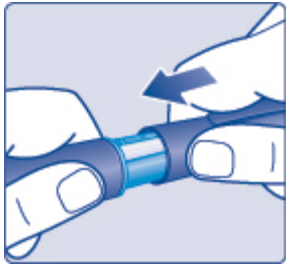


(Figure S)

- o **Do not** store the Pen with the needle attached. Storing without the needle attached helps prevent leaking, blocking of the needle, and air from entering the Pen.

Step 16:

- Replace the Pen cap by pushing it straight on (See Figure T).



(Figure T)

After your injection:

- Put your used RYZODEG 70/30 FlexTouch Pen and needles in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and Pens in your household trash.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - o made of a heavy-duty plastic
 - o can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
 - o upright and stable during use
 - o leak-resistant
 - o properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. Do not reuse or share needles or syringes with another person. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

How should I store my RYZODEG 70/30 FlexTouch Pen?

Before use:

- Store unused RYZODEG 70/30 FlexTouch Pens in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze RYZODEG 70/30. **Do not** use RYZODEG 70/30 if it has been frozen.
- Unused Pens may be used until the expiration date printed on the label, if kept in the refrigerator.

Pen in use:

- Store the Pen you are currently using out of the refrigerator below 86°F.
- Keep RYZODEG 70/30 away from heat or light.
- The RYZODEG 70/30 FlexTouch Pen you are using should be thrown away after 28 days, even if it still has insulin left in it and the expiration date has not passed.

General Information about the safe and effective use of RYZODEG 70/30.

- **Keep RYZODEG 70/30 FlexTouch Pens and needles out of the reach of children.**

This label may not be the latest approved by FDA.
For current labeling information, please visit <https://www.fda.gov/drugsatfda>

- **Always** use a new needle for each injection.
- **Do not** share RYZODEG 70/30 FlexTouch Pens or needles with other people. You may give other people a serious infection, or get a serious infection from them.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Novo Nordisk A/S
DK-2880 Bagsvaerd, Denmark

Revised: 09/2015



For more information go to www.ryzodeg7030.com

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RYZODEG[®]
70/30
FlexTouch[®]
100 units/mL
Read before first use

